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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
MAR 81 M J TOPPER, M H WEEKS
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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-37575 AND AI3-37576
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0190-81 AND 75-51-0191-81
OCTOBER 1978 - JANUARY 1981

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USAEHA-75-51-0190-81, USAEHA-75-51-0191-81

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READ INSTRUCTIONS BEFORE COMPLETING FORM

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7. AUTHOR(s):
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MAURICE H. WEEKS

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Aberdeen Proving Ground, MD 21010

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Topical Hazard Evaluation	Skin irritation
USDA Proprietary Chemicals	Eye irritation
AI3-37575	Photochemical irritation
AI3-37576	Guinea pig sensitization
Candidate repellents	ALD

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Preliminary hazard evaluations of AI3-37575 and AI3-37576 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical-grade chemicals have the potential to cause mild injury to the cornea, and some damage to the conjunctiva. However neither demonstrated potential for causing skin or photochemical irritation, did not sensitize guinea pigs, and did not indicate an acute ingestion hazard. It was recommended that both compounds be approved for further testing as candidate insect repellents.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

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584-3980

REPLY TO ATTENTION OF
HSE-LT-T/WP

25 MAR 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-37575 and AI3-37576, US Department of Agriculture Proprietary Chemicals, Study Nos. 75-51-0190-81 and 75-51-0191-81, October 1978-January 1981

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluations of AI3-37575 and AI3-37576 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical-grade chemicals have the potential to cause mild injury to the cornea, and some damage to the conjunctiva. However neither demonstrated potential for causing skin or photochemical irritation, did not sensitize guinea pigs, and did not indicate an acute ingestion hazard. It was recommended that both compounds be approved for further testing as candidate insect repellents.

FOR THE COMMANDER:

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO ATTENTION OF

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS AI3-37575 AND AI3-37576 US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS STUDY NOS. 75-51-0190-81 AND 75-51-0191-81 OCTOBER 1978 - JANUARY 1981

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 13 October 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37575 and AI3-37576.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate repellents AI3-37575 and AI3-37576 were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*†

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* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.
† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0190-81 and 75-51-0191-81, Oct 78 - Jan 81

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits. 0.5 mL technical-grade chemical applied to each of six rabbits.	Chemicals AI3-37575 and AI3-37576 did not cause any irritation of the intact skin or of the skin surrounding an abrasion (refer to Appendices B and C for details).	USAEHA Category I (ref Appendix A)
EYE IRRITATION STUDIES		
Rabbits		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemicals AI3-37575 and AI3-37576 produced mild injury to the cornea and in addition mild injury to the conjunctiva in six of six rabbits (refer to Appendices D and E for details).	USAEHA Category C (ref Appendix A)
APPROXIMATE LETHAL DOSE (ALD)		
Oral		
Rats (male)-no diluent	AI3-37575 ALD = 4300 mg/kg AI3-37576 ALD = 2900 mg/kg	Neither chemical presents an acute lethal hazard from accidental ingestion.

Study Nos. 75-51-0190-81 and 75-51-0191-81, Oct 78 - Jan 81

Test	Results	Interpretation
PHOTOCHEMICAL SKIN IRRITATION STUDIES		
Rabbits		
A single 0.05 mL application of a 25 percent (w/v) solution of each chemical and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25 percent solution of AI3-37575 and a 25 percent solution of AI3-37576 in ethanol did not cause a photochemical irritation reaction under test conditions (refer to Appendices F and G for details).	Chemicals AI3-37575 and AI3-37576 did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.
Control		
Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	

Study Nos. 75-51-0190-81 and 75-51-0191-81, Oct 78 - Jan 81

Test	Results	Interpretation
SENSITIZATION STUDIES		
Guinea Pigs (Male)		
Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of AI3-37575 and AI3-37476 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline		
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with ID injections of each test chemical.	Challenge doses of chemicals AI3-37575 and AI3-37576 did not produce a sensitization reaction (refer to Appendices H and I for details).	Chemicals AI3-37575 and AI3-37576 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer

Study Nos. 75-51-0190-81 and 75-51-0191-81, Oct 78 - Jan 81

5. CONCLUSION. Technical-grade chemicals AI3-37575 and AI3-37576 showed a potential for causing mild eye irritation, but caused no other irritation reactions from skin, photochemical or sensitization testing and do not present an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37575 and AI3-37576 be approved for further testing as candidate insect repellents.

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APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

APPENDIX B

COMPOUND: AI3-375-75, USDA Proprietary Chemical

USAEHA Study No. 75-51-0190-81

PRIMARY SKIN EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHA TOXICITY CATEGORY
I

CONDITIONS - 0.5 ml technical grade chemical applied to intact and abraded skin for 24 hours

	Time of Observation (Hours)	Response Rabbit No. 1	2	3	4	5	6	Mean Score	Comments
Erythema & Eschar									
Intact Skin	24		0		0		0	0	
Intact Skin	72		0		0		0	0	
Abraded Skin	24	0		0		0		0	
Abraded Skin	72	0		0		0		0	
					Subtotal			0	
Edema Formulation									
Intact Skin	24		0		0		0	0	
Intact Skin	72		0		0		0	0	
Abraded Skin	24	0		0		0		0	
Abraded Skin	72	0		0		0		0	
					Subtotal			0	
					Total			0	

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APPENDIX C

COMPOUND: AI3-375-76, USDA Proprietary Chemical

USAEHA Study No. 75-51-0190-81

PRIMARY SKIN EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHATOXICITY CATEGORY
I

CONDITIONS - 0.5 ml technical grade chemical applied to intact and abraded skin for 24 hours

	Time of Observation (Hours)	Response Rabbit No. 89	90	92	93	94	95	Mean Score	Comments
Erythema & Eschar									
Intact Skin	24	0		0		0		0	
Intact Skin	72	0		0		0		0	
Abraded Skin	24		0		0			0	
Abraded Skin	72		0		0			0	
					Subtotal			0	
Edema Formulation									
Intact Skin	24	0		0		0		0	
Intact Skin	72	0		0		0		0	
Abraded Skin	24		0		0		0	0	
Abraded Skin	72		0		0		0	0	
					Subtotal			0	
					Total			0	

USAEHA FORM 26-3, 21 JUN 79 (HSE-LT)

Study Nos. 75-51-0190-81 and 75-51-0191-81, Oct 78 - Jan 81

APPENDIX D

COMPOUND: AI3-37575, USDA Proprietary Chemical — Study No. 75-51-0190-81

ACUTE EYE EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHA TOXICITY CATEGORY
C

CONDITIONS - Single 24-hour application of 0.1 ml technical grade chemical to one eye of each rabbit

Time of Reading Hrs-Days	Structure	Scores Rabbit No. 1	2	3	4	5	6	Mean Score	Comments
24	cornea	15	5	10	20	10	15	12.50	
	iris	0	0	5	0	0	0	0.83	
	conjunctivae	2	0	6	14	8	4	5.67	
48	cornea	5	5	0	15	5	10	6.67	
	iris	0	0	0	5	0	5	1.67	
	conjunctivae	0	0	0	8	0	8	2.67	
72	cornea	0	0	0	5	0	5	1.67	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	0	0	8	0	0	1.33	
7-days	cornea	0	0	0	0	0	0	0	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	0	0	0	0	0	0	

APPENDIX E

COMPOUND: AI3-37576, USDA Proprietary Chemical

USAEHA Study No. 75-51-0191-81

ACUTE EYE EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHA TOXICITY CATEGORY

C

CONDITIONS - Single 24 hour application of 0.1 ml technical grade chemical to one eye of each rabbit

Time of Reading Hrs-Days	Structure	Scores Rabbit No. 7	8	9	10	11	12	Mean Score	Comments
24	cornea	5	10	20	20	15	20	15.00	
	iris	0	0	0	0	0	5	0.83	
	conjunctivae	6	10	6	8	6	6	7.00	
48	cornea	0	5	15	10	10	20	10.0	
	iris	0	5	5	0	0	0	1.67	
	conjunctivae	0	8	6	4	0	4	3.67	
72	cornea	0	5	5	5	0	15	5.00	
	iris	0	5	0	0	0	0	0.83	
	conjunctivae	0	8	6	4	0	4	3.67	
7-days	cornea	0	0	0	0	0	0	0	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	0	0	0	0	0	0	

USAEHA FORM 26-2, 21 JUN 79 (HSE-LT)

APPENDIX F

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37575, USDA Proprietary Chemical

USAEHA STUDY NO. 75-51-0190-81

COMMENTS:

PHOTOCHEMICAL IRRITATION PROCEDURE: Single application (0.05 ml) of a 25 percent solution of chemical and of a 10 percent oil of Bergamot solution (pos. control) in 95 percent ethanol to intact skin of six rabbits. Then exposed to UV light for 30 minutes.

	MEAN SKIN IRRITATION SCORE							
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
Observation Time	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	8	1	4	0	16	18	5	3
48 Hours	5	0	4	0	15	17	2	2
72 Hours	5	0	4	0	11	7	0	0
TOTAL	18	1	16	0	42	42	7	5
Mean Irritant Responses	1.0	0.06	0.89	0	2.33	2.33	0.39	0.27
Net Score	0.1	0.06			1.94	2.05		

AEHA Form 62, 1 Feb 81 (HSE-LT)

APPENDIX G

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37576, USDA Proprietary Chemical

USAEHA STUDY NO. 75-51-0191-81

COMMENTS:

PROCEDURE: Single application (0.05 ml) of a 25 percent solution of chemical and of a 10 percent solution of oil of Bergamot solution (pos control) in 95 percent ethanol to intact skin of six rabbits. Then exposed to UV light for 30 minutes.

	MEAN SKIN IRRITATION SCORE							
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
Observation Time	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	5	2	3	2	20	19	8	5
48 Hours	4	2	3	2	19	22	10	5
72 Hours	0	0	0	0	13	14	1	0
TOTAL	9	4	6	4	52	55	19	10
Mean Irritant Responses	0.5	0.22	0.33	0.22	2.89	3.06	1.06	.56
Net Score	0.17	0			1.83	2.50		

AEHA Form 62, 1 Feb 81 (HSE-LT)

APPENDIX H

COMPOUND: AI3-375-75, USDA Proprietary Chemical USAEHA Study No. 75-51-0190-81

GUINEA PIG SENSITIZATION
MALE
HARTLEY STRAIN

Substance: AI3-37575

Identify: USDA Proprietary Chemical

Positive Control: Dinitrochlorobenzene

Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores				Comments
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	437	581	0	0	0	15.9	
Positive Control	441	601	0	0	10.4	344	
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores				
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	-	-	0	0	0	1.6	
Positive Control	-	-	0	0	6.6	260	
							Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing

USAEHA FORM 26-4, 9 JUL 79 (HSE-LT)

APPENDIX I

COMPOUND: AI3-73576, USDA Proprietary Chemical USAEHA Study No. 75-51-0191-81

GUINEA PIG SENSITIZATION
MALE
HARTLEY STRAIN

Substance: AI3-37576

Identify: USDA Proprietary Chemical

Positive Control: Dinitrochlorobenzene

Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores				Comments
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	437	603	0	0	0	0	
Positive Control	441	601	0	0	10.4	344	

Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores				
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	-	-	0	0	0	0	
Positive Control	-	-	0	0	6.6	260	

Final Scores
>100 - Strong Sensitizing
25-100 - Mild Sensitizing
<25 - No Sensitizing

USAEHA FORM 26-4, 9 JUL 79 (HCF-LT)

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